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ORIGINAL ARTICLE

The importance of measuring macroprolactin in the differential diagnosis of hyperprolactinemic patients

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Abstract This study investigated the differences in clinical and laboratory features as well as treatment response in 70 outpatients with macroprolactinemia and monomeric hyperprolactinemia treated with dopamine agonists. After precipitation of the patients' serum samples with poly-ethylene-glycol (PEG), serum prolactin (PRL) levels were measured. We also measured serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol for women and testosterone for men. Clinical symptoms and signs were recorded. All patients received brain magnetic resonance imaging (MRI). After excluding patients with macroadenoma, 66 patients were treated with the dopamine agonist cabergoline. After 1 year, the clinical responses to cabergoline were recorded and PRL levels measured. Of the initial 70 patients with hyperprolactinemia, 15 patients (21.4%) were found to have macroprolactinemia, while the rest had monomeric hyperprolactinemia. The two groups did not differ with regard to galactorrhea, menstrual disturbances or impotence. There were no significant group differences in serum LH, FSH, estradiol or testosterone levels. Patients with macroprolactinemia, however, had a significantly lower infertility rate than those with true hyperprolactinemia (6.7% vs. 32.7%, $p = 0.005$). A greater percentage of macroprolactinemic patients had normal MRI pituitary images than those with hyperprolactinemia (73.3% vs. 34.5%, $p = 0.029$). Compared to those with true hyperprolactinemia, patients with macroprolactinemia were found to have no significant changes in clinical features and PRL levels after 1 year of cabergoline therapy (after PEG precipitation, pre- and post-PRL levels: 59.3 ± 100.2 to 13.8 ± 9.5 ng/mL vs. 6.1 ± 5.3 to 5.1 ± 4.3 ng/mL, $p = 0.002$). In conclusion, while macroprolactinemia is a common cause of hyperprolactinemia, many clinical and laboratory features cannot be used reliably to differentiate macroprolactinemia from true hyperprolactinemia. Routine screening for all hyperprolactinemic sera with PEG might prevent the unnecessary use of image studies and medical treatments for people with hyperprolactinemia.

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Introduction

Hyperprolactinemia can be caused by physiological or pathological conditions that lead to the hypersecretion of PRL in the lactotroph cells. Physiological conditions include pregnancy and lactation, while pathological conditions may include a hypothalamic tumor, lactotroph adenoma, the use of dopamine-2 receptor antagonist drugs or hypothyroidism [1,2]. Hyperprolactinemia is also the most common abnormality of the hypothalamic−pituitary axis and the most frequent manifestation of functional pituitary adenomas [1]. It has been associated with the suppression of gonadotropin secretion and decreases in sex hormones in men and women, resulting in sexual dysfunction, such as aspermatogenesis in men and anovulation in women, both of which will prompt physicians to measure prolactin (PRL) levels to confirm suspicions of this disease.

The detection of serum PRL may be difficult when there is interference between macroprolactin and PRL assays [3,4]. Human serum PRL appears in three major molecular forms: the biologically and immunologically active monomeric PRL (little PRL, 23 kDa, 85−95%), the biologically inactive dimeric PRL (big PRL, 50−60 kDa, 5−15%), and low activity tetrameric PRL (big big PRL, 150−170 kDa, <1%) [5]. Macroprolactin, however, is a complex of dimeric and tetrameric PRL [6,7]. While macroprolactinemia is defined as a preponderance of macroprolactin in hyperprolactinemic sera [8], its clinical significance is controversial. In most studies [8−10], patients with macroprolactinemia always have normal menstruation cycles, spontaneous conception and mild galactorrhea. One study suggests that a misdiagnosis of macroprolactinemia as monomeric hyperprolactinemia might lead to unnecessary and unhelpful pituitary exploration and treatment [11]. Some previous studies finding bioactivity *in vivo*, however, suggest that macroprolactinemia could cause galactorrhea, menstrual irregularities, infertility and erectile dysfunction [2,12,13]. It has also been suggested that treatment with dopamine agonists (DAs) could lower the serum macroprolactin levels [2,12].

The aim of this study was to investigate the prevalence of macroprolactinemia in people from Taiwan, differentiate the clinical and laboratory features of macroprolactinemia and monomeric hyperprolactinemia, and to evaluate the differences in these two groups' responses to treatment with a DA.

Methods

Participants

Between October 2009 and February 2011, we enrolled 70 patients (61 women and nine men; aged 39 ± 10 years) form our outpatient clinics at the Endocrinology, Neurosurgery and Gynecology Department in Kaohsiung Chang Gung Memorial Hospital (CGMH) who were diagnosed as having hyperprolactinemia (PRL serum level ≥18.0 ng/mL for men and ≥7.0 ng/mL for women). We excluded patients with other major diseases that could induce elevation of serum globulin concentrations, such as renal insufficiency (creatinine >1.4 mg/dl), adrenal insufficiency, primary hypothyroidism, polycystic ovary syndrome, IgG myeloma and polyclonal hypergammaglobulinemia due to HIV infection. We also excluded any patients who were pregnant, breast feeding or taking a drug that could lead to an increase PRL levels. Poly-ethylene-glycol (PEG) was used to analyze all serum samples. We also measured serum levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol in women and testosterone in men.

All patients underwent magnetic resonance imaging (MRI) studies. We excluded the patients with macroadenoma found by MRI (tumor diameter >1.0 cm) because they would probably receive surgery later on. Of the patients with monomeric hyperprolactinemia, four had macroadenomas. No patients diagnosed with macroprolactinemia had a tumor. After exclusion, we were left with 66 patients that we could treat with a DA. These participants consisted of 58 women and eight men (aged 38.2 ± 10.4 years). Each received cabergoline (1 mg/week) in tablet form. Drug compliance was calculated by the number of surplus tablets they returned to us at the end of each 3-month prescription period. No patient to returned >10% of the prescribed doses. After 12 months, we measured their serum PRL levels and evaluated changes in their clinical features. The evaluation was performed by the same physicians that they had initially visited. The clinical features analyzed in this study were oligomenorrhea, amenorrhea, galactorrhea, impotence and infertility. All the clinical features were confirmed by a gynecologist and urologist, and met the criteria for diagnosis.

This study was conducted according to the guidelines outlined in the declaration of Helsinki and the protocol for this study was approved by the CGMH Ethics Committee.

Tests

Serum estradiol, testosterone, LH and FSH were measured using a commercially-available immunoradiometric assay (^{125}I IRMA, IMMUNOTECH, Beckman Coulter Company, USA), as was PRL (^{125}I IRMA, IMMUNOTECH, Beckman Coulter Company), with a reference range of 1.0−18.0 ng/ml for men and 1.0−27.0 ng/ml for women. The low, normal and high ranges for the coefficient of variation (CV) and intra-assay CV were 8.0%, 6.7% and 6.2%, and 1.6%, 2.8% and 2.8%, respectively.

After PEG precipitation, we measured the presence of macroprolactin in hyperprolactinemic sera using a PRL assay. To do this, 250 uL of serum was mixed with an equal volume of PEG (250 g/L, molecular mass 6000 kDa, product no. 528877, Merck Ltd, Darmstadt, Germany) and incubated for 10 minutes at room temperature. The suspension was clarified by centrifugation at 1800 g for 30 minutes. The supernatant was analyzed for prolactin. Macroprolactinemia was determined by measuring the PRL serum level before and after PEG precipitation. As in previous studies [14,15], macroprolactinemia was defined as having a PRL recovery of ≤40% after PEG precipitation and monomeric (true) hyperprolactinemia was defined as having a recovery of >40%. Every sample was assayed three times and an average value was assigned.

Statistical analysis

Differences between the groups were analyzed using a non-parametric Wilcoxon test. Differences between time points in treatment were calculated using repeated measures of the general linear model. All data are reported as means ± standard deviation. A probability value of <0.05 was regarded to be significant. All statistical operations were performed using the Statistical Package for Social Science program (SPSS for Windows, Version 11.5; SPSS, Chicago).

Results

Changes in PRL after PEG precipitation

As can be seen in Table 1, which gives a summary of different variables between macroprolactinemia and monomeric hyperprolactinemia after PEG precipitation, 15 of the 70 patients (21.4%) with high PRL levels were found to have macroprolactinemia. There was no difference in age or gender between the two groups. After PEG precipitation, all samples of hyperprolactinemic sera had decreases in PRL, though the PRL level in most of the macroprolactinemic patients remained within normal limits. The mean serum prolactin levels after PEG precipitation in macroprolactinemic patients and true hyperprolactinemic patients were 6.1 ± 5.3 ng/mL and 62.2 ± 160.2 ng/mL, respectively ($p = 0.003$).

Clinical manifestations and laboratory features

Table 1 shows that macroprolactinemia and monomeric hyperprolactinemia did not differ with regard to the following clinical features:

- galactorrhea (20% vs. 31%);
- menstrual disturbances (oligomenorrhea or amenorrhea, 66.7% vs. 77.6%); and
- impotence (100% of men in both groups).

Patients with macroprolactinemia had a significantly lower infertility rate than those with monomeric hyperprolactinemia (6.7% vs. 32.7%, $p = 0.005$). Laboratory work showed no significant group differences in serum FSH (9.13 ± 6.54 vs. 9.77 ± 7.06 mIU/ml), LH (13.38 ± 13.87 vs. 14.87 ± 9.92 pg/ml), estradiol (in women, 28.23 ± 12.12 vs. 30.46 ± 11.22 pg/ml) and testosterone (in men, 2.48 ± 4.49 vs. 2.39 ± 3.17 ng/ml).

Image findings

MRI findings revealed that four patients in the macroprolactinemic group (26.7%) had pituitary lesions. Three of these patients had a microadenoma and one had empty sella lesions. Four of the 55 monomeric hyperprolactinemic patients (7%, three women and one man) had macroadenomas, 32 (58.2%) had microadenomas, and 19 (34.5%) were not found to have any pituitary lesions. A greater percentage of macroprolactinemic subjects had normal pituitary images (73.3% vs. 34.5%, $p = 0.029$).

Treatment response

This study found no apparent change in clinical features (including infertility) in the macroprolactinemic group, but there were changes in the symptoms experienced by the patients with monomeric hyperprolactinemia patients. After 1 year, these patients experienced a reduction in galactorrhea (from 31.4% to 2.0%), menstrual disturbances (from 80.4% to 6.5%), impotence (in men, from 100% to 20%)

Table 1 The clinical characteristics of patients with macroprolactinemia and true hyperprolactinemia.

Characteristics	Macroprolactinemia ($n = 15$)	True hyperprolactinemia ($n = 55$)	p-value
Sex ratio (F/M)	(12/3)	(49/6)	—
Age (yr)	37.5 ± 11.5	39.5 ± 9.7	NS
Basal PRL (ng/mL)	63.3 ± 59.2 (22.5–261)[a]	132.6 ± 312.6 (27.0–2278)[a]	0.071
Post PEG PRL (ng/mL)	6.1 ± 5.3 (1.9–24.7)[a]	62.2 ± 160.2 (12.4–1267)[a]	0.003
Normal MRI	11 (73.3%)	19 (34.5%)	0.029
Galactorrhea	3 (20%)	17 (31.0%)	NS
Menstrual disorder (oligo- or amenorrhea)	8 (66.7%)	38 (77.6%)	NS
Impotence (men)	3 (100%)	6 (100%)	NS
Infertility	1 (6.7%)	18 (32.7%)	0.005
FSH (mIU/ml)[b]	9.13 ± 6.54	9.77 ± 7.06	NS
LH (pg/ml)[b]	13.38 ± 13.87	14.87 ± 9.92	NS
Estradiol (pg/ml)[c]	28.23 ± 12.12	30.46 ± 11.22	NS
Testosterone (ng/ml)[d]	2.48 ± 4.49	2.39 ± 3.17	NS

Key: MRI = magnetic resonance imaging, NS = not significant, PEG = poly-ethylene-glycol, PRL = prolactin.
[a] range of prolactin serum level.
[b] follicle-stimulating hormone and luteinizing for both sexes.
[c] estradiol for women.
[d] testosterone for men.

and infertility (from 27.4% to 3.9%). All of these reductions, shown in Table 2, were significant ($p < 0.001$). The PRL levels decreased to within the normal range in all patients with monomeric hyperprolactinemia, with basal levels ranging from 130.5 ± 210.6 ng/mL to 15.2 ± 10.2 ng/mL vs. post-PEG levels from 59.3 ± 100.2 ng/mL to 13.8 ± 9.5 ng/mL ($p < 0.001$). There were no clear improvements, however, in the macroprolactinemic patients in whom basal levels ranged from 63.3 ± 59.2 ng/mL to 60.4 ± 50.8 ng/mL and post-PEG levels ranged from 6.1 ± 5.3 ng/mL to 5.1 ± 4.3 ng/mL. Compared to the patients with monomeric hyperprolactinemia, those with macroprolactinemia had higher rate of galactorrhea (13.3% vs. 2.0%, $p < 0.001$), menstrual disturbances (50.0% vs. 6.5%, $p < 0.001$), impotence (in men, 100% vs. 20%, $p < 0.001$) and infertility (6.7% to 3.9%, $p = 0.03$), even after treatment with cabergoline.

Discussion

Due to no specific symptoms and signs, macroprolactinemia may lead to unnecessary pituitary exploration and treatment and has not attracted much attention since the first case of macroprolactinemia was reported in 1981 [16]. This may be due to differences in the cut-off values of PRL recovery after PEG precipitation, race, and equivocal clinical symptoms. This study, the first of its kind to be performed in Taiwan, found the prevalence of macroprolactinemia to be 21.4% in our hyperprolactinemic patients, which is consistent with the findings of previous investigations in other countries, the ratio being between 10% and 46% [2,3,12,14,17]. In our patients, by comparison with gel-filtration chromatography, the gold standard method, a PRL recovery $\leq$40% was defined as macroprolactinemia. This is considered a reliable diagnostic criterion. As in previous studies [14,15], PRL recovery >40% was classified as true or monomeric hyperprolactinemia. In some studies [18,19], PRL recovery of between 40% and 50% necessitated gel filtration chromatography to confirm the presence of macroprolactin. However, in our study, none of the patients enrolled had a recovery rate within this band, so we did not need to carry out such time-consuming and expensive tests.

For many years, macroprolactinemia was regarded to be asymptomatic among hyperprolactinemic patients [8,9]. In recent studies [2,12,13] as well as ours in investigation, however, the same symptoms have been to found to be as common in macroprolactinemia as in true hyperprolactinemia. Such symptoms were non-specific. About half of our macroprolactinemia patients were symptomatic. The groups did not differ with regard to the frequency of galactorrhea, menstrual disturbances or impotence. Infertility was significantly more prevalent in the patients with true hyperprolactinemia, and this may be the only thing distinguishing cases of macroprolactinemia from true hyperprolactinemia. Despite this, a diagnosis of infertility is more difficult to render and requires a longer observation time than other symptoms, so it may not serve as a reliable or practical diagnostic clue. The overlap of clinical features therefore still prohibits us from being able to use symptoms to distinguish between macroprolactinemia and true hyperprolactinemia.

Due to the reduced ability of macroprolactin unable to suppress the hypothalamic– pituitary–gonadal axis, levels of LH have previously been reported to be significantly higher in macroprolactinemic patients [20]. As with de Soárez et al. [21], we found no significant difference in serum LH and FSH levels, estradiol levels in women or testosterone levels in men between the two groups. The results of our study may be confounded, however, by the variable biological activity of macroprolactin or the pulsatile secretion of these hormones. A number of studies on macroprolactin biological activity have been performed [22–25]. Few have revealed similar *in vitro* activity as true hyperprolactinemia, but most have shown less activity [23,24]. It has been postulated that, although macroprolactin has the ability to present monomeric prolactin-like activity *in vitro*, its bioavailability would be negligible *in vivo* due to its high molecular weight [26,27]. Macroprolactin should be confined to the vascular system but several studies using a Nb2 rat lymphoma cell bioassay have shown macroprolactin to have variable biological activity *in vivo* [8,28,29]. Another study has suggested that this might be due to macroprolactin's ability to intermittently dissociate from IgG [28]. This finding is consistent with our data, showing the overlap of clinical and biochemical features of the two entities.

Table 2 A comparison of changes in clinical characteristics between patients with macroprolactinemia and monomeric hyperprolactinemia after 1 year of dopamine agonist therapy.

Characteristics	Macroprolactinemia ($n = 15$, F/M = 12/3)		True hyperprolactinemia ($n = 51$, F/M = 46/5)		p-value[a]
	Before treatment	After treatment	Before treatment	After treatment	
Basal PRL (ng/mL)	63.3 ± 59.2	60.4 ± 50.8	130.5 ± 210.6	15.2 ± 10.2*	0.004
Post-PEG PRL (ng/mL)	6.1 ± 5.3	5.1 ± 4.3	59.3 ± 100.2	13.8 ± 9.5*	0.002
Galactorrhea	3 (20%)	2 (13.3%)	16 (31.4%)	1 (2.0%)*	<0.001
Menstrual disorder	8 (66.7%)	6 (50%)	37 (80.4%)	3 (6.5%)*	<0.001
Impotence (men)	3 (100%)	3 (100%)	5 (100%)	1 (20%)*	<0.001
Infertility	1 (6.7%)	1 (6.7%)	14 (27.4%)	2 (3.9%)*	0.03

Differences between the treatment time points were calculated using repeated measures of general linear model.
*tests of intrasubject contrasts in the group after 1 year of treatment with cabergoline and $p < 0.001$.
Key: PEG = poly-ethylene-glycol, PRL = prolactin.
[a] tests of intersubject effects.

Some investigations [2,30,31] have reported that 6–22% of their macroprolactinemic patients had pituitary adenomas. Pituitary imaging in the study by Leslie et al. [14] found that four out of the 55 macroprolactinemic patients had microadenomas, but none had macroadenomas. In our study, the patients with hyperprolactinemia all received the same imaging studies before PEG precipitation. Macroprolactinemic patients had a higher rate of negative MRI findings than those with true hyperprolactinemia ($p = 0.029$). Furthermore, we did not find any instance of pituitary macroadenomas in our macroprolactinemic patients, and only three patients (20%) were found to have microadenomas. The MRI examinations performed on the macroprolactinemic group could therefore be considered unnecessary.

In a study by Alfonso et al. [31], about 40% of patients in the macroprolactin group were treated with a DA, of which total prolactinemia was normalized in 28%. The study was retrospective, however, with only a small number of patients enrolled and it did not measure macroprolatin levels. As far as we know, no previous studies have evaluated the therapeutic efficiency of DAs in the treatment of macroprolactinemia. All of our macroprolactinemic patients were treated with the same dose of cabergoline for the same period of time. Before cabergoline treatment, most of these patients had post-PEG precipitating PRL levels within the normal range. After treatment, the total PRL levels of the patients were still not normalized. After PEG precipitation, this group had no apparent change in PRL levels.

Macroprolactinemia has been considered a cause of resistance to DAs [32,33]; therefore misdiagnosis may result in unnecessary and unhelpful therapy as well as unnecessary costs. Conversely, a three-case study [34] reported that DA treatment decreased the serum levels of both monomeric PRL and macroprolactin and improved hyperprolactinemic symptoms. Our study found DA therapy to be unnecessary and unhelpful. Spontaneous improvement or resolution may occur in some patients with macroprolactinemia, and may not be related to DA treatment.

One study [30] reported that cost savings could be achieved through diminished requests for imaging procedures, a reduced number of DA prescriptions and even cases of pituitary surgery after routine screening for macroprolactin, although de Soárez et al. [21] did not come to the same conclusion. The differences in results might be because many of the patients in the former study received some tests outside their institution that were not included in the total cost. Whether the performance of routine macroprolactin screening can actually reduce inappropriate investigation and reduce costs still requires long-term study.

Conclusion

Although macroprolactinemia was first reported 30 years ago, few physicians in Taiwan are familiar with it and believe that it can be evaluated in the same way it is in patients with hyperprolactinemia. Our method of detection was confirmed by the gold standard method, gel-filtration chromatography, and excluded equivocal data. We conclude that neither clinical nor laboratory features can be used to reliably differentiate between macroprolactinemia and true hyperprolactinemia and that a misdiagnosis of hyperprolactinemia may lead to inappropriate investigation with MRI and unnecessary surgery or medical treatment with DA. Routine screening for all hyperprolactinemic sera with PEG may therefore help to reduce the number of misdiagnoses and instances of unnecessary treatment. The high prevalence of macroprolactinemia in Taiwan makes this a priority. Physicians here might want to encourage laboratories to make the measurement of macroprolatin a routine study.

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